DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]This invention relates to the skin external preparations containing tyrosinase inhibitor and this tyrosinase inhibitor containing the Matsuki hide extract.
[0002]
[Description of the Prior Art]Melanin generates silverfish and a freckle by operation of a tyrosinase from tyrosine which is an essential amino acid in the pigment cell activated in response to the abnormalities and ultraviolet rays of hormonal secretion, and in order that this may deposit to skin structure, they are produced. It becomes a trigger that tyrosine receives an operation of a tyrosinase, and generation of melanin takes place, when this changes to black melanin in response to the still more enzymatic or nonenzymatic oxidation. Therefore, it is important for control of melanin generation to inhibit an operation of the tyrosinase which is the 1st step of a reaction. Therefore, in order to prevent generation of melanin, in the field of cosmetics or foodstuffs, various substances which check an operation of a tyrosinase are used from the former, or are studied. Although ascorbic acid, hydroquinone, kojic acid, etc. are mentioned as the typical thing, The thing of natural material origin with safety high also about the tyrosinase inhibitor which prevents melanin generation has come to be called for as concern about the safety of foodstuffs or cosmetics increases in recent years.
[0003]
[Problem(s) to be Solved by the Invention]This invention is made in view of the above-mentioned situation, and the purpose of this invention is to provide the skin external preparations containing new tyrosinase inhibitor and it of natural material origin with high safety.
[0004]
[Means for Solving the Problem]As a result of looking for a natural material which checks an

operation of a tyrosinase, this invention persons found out that the Matsuki hide extract checked an operation of a tyrosinase, and resulted in completion of this invention. This invention is tyrosinase inhibitor containing the Matsuki hide extract. In a mode of desirable operation, said Matsuki hide extract is tyrosinase inhibitor which contains an oligomeric pro anthocyanidin (oligomeric proanthocyanidin) 20% of the weight or more. In another desirable embodiment, tyrosinase inhibitor of this invention is tyrosinase inhibitor in which said Matsuki hide extract contains catechin (catechin) 5% of the weight or more further. This invention is the skin external preparations containing the above-mentioned tyrosinase inhibitor.

[0005]

[Embodiment of the Invention]Hereafter, tyrosinase inhibitor of this invention is explained. The following explanation cannot limit this invention and can change it variously within the limits of the meaning of this invention.

[0006]Tyrosinase inhibitor of this invention contains the Matsuki hide extract. As a Matsuki hide extract, the France seashore pine (Pinus Martima), Bark extracts, such as ANEDA of a larch, a clo pine, a Japanese red pine, HIMEKOMATSU, GOYOUMATSU, Pinus koraiensis, a high pine, RYUUKYUUMATSU, UTSUKUSHIMATSU, the Pinus palustris, SHIROMATSU, and the Quebec district in Canada, are used preferably. Especially, the bark extract of the France seashore pine (PinusMartima) is used preferably.

[0007]The France seashore pine says the oceanic pine grown to a part of Atlantic coast in south France. The bark of this France seashore pine contains the physiologically active components of a pro anthocyanidin (proanthocyanidin), organic acid, and others, etc., and it is known that the pro anthocyanidin of the flavonoids which are basic components has a strong antioxidant action which removes active oxygen.

[0008]The Matsuki hide extract is obtained by extracting the bark of the above-mentioned pine with water or an organic solvent. When using water, warm water and hot water are used. As an organic solvent used for extraction, methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, butane, acetone, Hexane, cyclohexane, propylene glycol, hydrous ethanol, The organic solvent permitted by manufacture of foodstuffs, such as hydrous propylene glycol, ethyl methyl ketone, glycerin, methyl acetate, ethyl acetate, diethylether, dichloromethane, edible oil and fat, and 1,1,1,2-tetrafluoro ethane, or drugs is used preferably. These water and an organic solvent may be used independently, and they may be used in combination. In particular, hot water, hydrous ethanol, hydrous propylene glycol, etc. are used preferably.

[0009]although the extraction method from the Matsuki hide does not have restriction in particular -- warming -- an extraction method, supercritical fluid extraction, etc. are used.

[0010]Supercritical fluid extraction is a method of extracting using the supercritical fluid which is a fluid in the state where the critical point (critical temperature, critical pressure) of the vapor-liquid of a substance was exceeded. As supercritical fluid, although carbon dioxide, ethylene,

propane, nitrous oxide (laughter gas), etc. are used, carbon dioxide is used preferably. In supercritical fluid extraction, the extraction process of extracting an objective component by supercritical fluid, and an objective component and the partition process which separates supercritical fluid are performed. In a partition process, any of the extraction separation by pressure variation, the extraction separation by a temperature change, and the extraction separation using adsorbent and an absorbent may be performed. Supercritical fluid extraction by an entrainer addition method may be performed. This method in an extraction fluid, for example Ethanol, propanol, n-hexane, By carrying out 2-20 W/V% (weight versus percent by volume) grade addition of acetone, other toluene and aliphatic series lower alcohol, aliphatic hydrocarbon, aromatic hydrocarbon, and the ketone, and performing supercritical fluid extraction by this fluid, The solubility to the extracting solvent of the extract made into the purposes, such as a pro anthocyanidin and catechin, is raised by leaps and bounds, or it is the method of reinforcing the selectivity of separation and is the method of obtaining the efficient Matsuki hide extract.

[0011]Circulation use of the advantage that it is applicable also to the substance deteriorated and disassembled at an elevated temperature since it can be operated at a comparatively low temperature, the advantage that an extraction fluid does not remain, and a solvent is possible for supercritical fluid extraction, a deliquoring process etc. can be skipped, and there is an advantage that a process becomes simple. Extraction of the Matsuki hide may be performed by liquid-carbon-dioxide batch process, the liquid-carbon-dioxide flowing-back method, the supercritical-carbon-dioxide flowing-back method, etc. Extraction of the Matsuki hide may combine two or more extraction methods. By combining two or more extraction methods, it becomes possible to obtain the Matsuki hide extract of various presentations.

[0012]Although two or more polycondensation polymer is contained in the Matsuki hide extract used for this invention, the degree of polymerization which makes a constitutional unit polycondensation polymer of a pro anthocyanidin, i.e., flavan-3-ol, and flavan 3,4-diol, What contains polycondensation polymer with a low degree of polymerization as a Matsuki hide extract is used preferably. That in which a degree of polymerization contains the condensation polymer (the amount object of 2 - 30) of 2-30 is preferred, that in which a degree of polymerization contains the condensation polymer (2 - decamer) of 2-10 is more preferred, and that in which a degree of polymerization contains the condensation polymer (2 - tetramer) of 2-4 is used still more preferably from excelling in skin permeability.

[0013]In this specification, the degree of polymerization made into a constitutional unit flavan-3-ol and/or flavan 3,4-diol among polycondensation polymer of a pro anthocyanidin the polymer of 2-4, It is called an oligomeric pro anthocyanidin (oligomeric proanthocyanidin and henceforth "OPC"). OPC is a kind of polyphenol, is a powerful antioxidant which vegetation makes and is intensively contained in the vegetable leaf, the bark, the hide of fruit, or the

portion of a seed. Specifically, it is contained in the seeds of a grape, the bark of a pine, the hide of a peanut, a ginkgo tree, the fruits of a black locust, a cowberry leaf, etc. It is known that OPC is contained also in the kola nuts of West Africa, the root of the latania of Peru, and Japanese green tea. Since OPC is an ungenerable substance in a human body, it is necessary to take in from the exterior. Since such OPC is an antioxidant, it has an improvement effect etc. of allergic constitutions, such as an effect, the arthritis, the atopic dermatitis, pollinosis, etc. which fall the percentage of risk of adult diseases, such as cancer, cardiopathy, and cerebral thrombosis. Furthermore, OPC prevents the lipoprotein in the inside of the effect of controlling the bacteria growth in the mouth besides an antioxidant action, and decreasing a plaque (dental plaque), the effect of recovering the elasticity of a blood vessel, and blood from receiving a damage by active oxygen, The damaged fat condenses to the wall of a blood vessel, and having the effect of preventing cholesterol from adhering, the effect of reproducing the vitamin E decomposed by active oxygen, an effect as an enhancement agent of vitamin E, etc. is known.

[0014]In this invention, the Matsuki hide extract which contains OPC 20% of the weight or more is used preferably. It is 30 % of the weight or more more preferably. Although the reason is unknown, if the Matsuki hide extract containing OPC of a low polymerization degree is used, a high anti-stress effect will be acquired as contrasted with the case where what has a high degree of polymerization is included. If stress collects, since it is useful to prevention of surface deterioration etc. for producing surface deterioration etc. to be known and to control stress, using tyrosinase inhibitor of this invention, It is useful as skin external preparations which it not only checks an operation of a tyrosinase directly, but have a beauty effect indirectly.

[0015]As for tyrosinase inhibitor of this invention, it is preferred to contain catechin (catechin) 5% of the weight or more. Catechin is extracted also from the Matsuki hide and it is contained in the Matsuki hide extract. That is, catechin may be extracted with OPC.

[0016]Catechin is general terms for polyhydroxy flavan-3-ol, and 3-galloyl derivative of GAROKATEKIN, AFUZEREKIN and (+)-catechin, or GAROKATEKIN besides (+)-catechin called catechin in a narrow sense is isolated from the natural product. As catechin, (+)-catechin, (-)-epicatechin, (+)-GAROKATEKIN, (-)-epigallocatechin, epigallocatechin gallate, epicatechin gallate, etc. are known. It is known that catechin has an elimination operation of cancer inhibition, arteriosclerosis prevention, control of the abnormalities in the fat metabolism, control of elevation of blood pressure, thrombus prevention, antiallergic, antivirotic, antibacterial properties, prevention of tooth decay, ozostomia prevention, the intestinal bacterial flora normalization effect, active oxygen, and a free radical, an antioxidant action, etc. It is known that catechin has the anti-diabetes-mellitus effect which controls a rise of blood sugar. There is activated character at the same time catechin rises under existence of OPC.

[0017]As for tyrosinase inhibitor of this invention, it is most preferred to use the Matsuki hide

extract which contains catechin 5% of the weight or more, and contains OPC 20% of the weight or more. Therefore, even if it is the Matsuki hide extract which contains OPC 20% of the weight or more, when catechin is not included 5% of the weight or more, it is preferred to add so that catechin may be contained 5% of the weight or more. That is, when the catechin content of the Matsuki hide extract is less than 5 % of the weight, it may add so that a catechin content may be 5 % of the weight or more. Even if it adds catechin to the Matsuki hide extract, it belongs under the category of the Matsuki hide extract said to this invention.

[0018]Although the Matsuki hide extract used for tyrosinase inhibitor of this invention is specifically prepared by the following methods, this is illustration and is not limited to this method.

[0019]The saturated solution 3L of sodium chloride extracts 1 kg of barks of the France seashore pine for 30 minutes at 100 **, and an extract is obtained (extraction process). Then, 500 ml of saturated solutions of sodium chloride wash the insoluble matter obtained by filtering an extract, and a penetrant remover is obtained (washing process). This extract and penetrant remover are set and the crude extract of the Matsuki hide is obtained. Subsequently, 250 ml of ethyl acetate is added to this crude extract, liquids are separated to it, and the ethyl acetate layer recovery process which collects ethyl acetate layers is performed 5 times. In this ethyl acetate layer recovery process, ethyl acetate layers are directly collected to the anhydrous sodium sulfate 200g. Then, this ethyl acetate layer is filtered, and vacuum concentration of the filtrate is carried out until it becomes the 1/5 original quantity. Filtration recovers the sediment which fills chloroform of 2L with the condensed ethyl acetate layer, and is produced by stirring. Then, after dissolving this sediment in 100 ml of ethyl acetate, the washing process which repeats twice operation of adding with chloroform of 1L and settling it again is performed. About 5-g Matsuki hide extract which contains catechin 5% of the weight or more by this method including OPC of 2 - a tetramer 20% of the weight is obtained.

[0020]The loadings of the Matsuki hide extract in this invention are 0.01 to 10.0 % of the weight preferably 0.005 to 20.0% of the weight as a dry matter among the external-preparations whole quantity. Since pharmaceutical-preparation-izing is difficult when the effect referred to as being less than 0.005 % of the weight by this invention is not fully demonstrated but exceeds 20.0 % of the weight, it is not desirable. Even if it blends 10.0% of the weight or more, the improvement in so big an effect is not found.

[0021]The ingredient usually used for tyrosinase inhibitor of this invention at skin external preparations, such as cosmetics and drugs, in addition to the above-mentioned essential ingredient, For example, other whitening agents, a moisturizer, an antioxidant, an oily component, a surface-active agent, a thickener, alcohols, a powder constituent, a coloring material, an aqueous ingredient, water, various skin nutrients, etc. can be blended suitably if needed.

[0022]If the skin external preparations of this invention are a thing of a gestalt used for skin external preparations conventionally [, such as ointment, cream, a milky lotion, a lotion, a pack, and baths,], any may be sufficient and a pharmaceutical form in particular will not ask.
[0023]
[Example]This invention is not restricted by this example, although an example is given to below and this invention is explained to it.
[0024](Performance evaluation test) The inhibiting activity of tyrosinase inhibitor of this invention using the ethanol extract of the Matsuki hide which contains catechin for OPC 5% of the weight 20% of the weight was evaluated as follows.
[0025](Preparation of a sample solution) Stage dilution was carried out using 1 / 15M phosphate buffer solution (pH-6.8), and tyrosinase inhibitor using the ethanol extract of the Matsuki hide was used as the sample solution.
[0026](Enzyme solution preparation) What diluted the tyrosinase (mushroom origin, Sigma) so that it might be set to 1100U/ml using 1 / 15M phosphate buffer solution was used as the enzyme solution.
[0027](Preparation of a substrate solution) What dissolved 3-mg DOPA(-)-3-(3, 4-dihydroxyphenyl)-L-alanine in a 10-ml phosphate buffer solution (pH-6.8) was used as the substrate solution.
[0028](Measurement of tyrosinase activity) A 0.1 ml enzyme solution, and 1 / 15M phosphate buffer solution 0.9-ml were added to a 1-ml sample solution, and it incubated for 10 minutes at 37 **. And after adding a 1-ml substrate solution and incubating for 5 minutes at 37 ** further, the absorbance at 475 nm was measured with the spectrophotometer. The tyrosinase inhibiting activity of this invention was evaluated using the absorption difference which deducted the absorbance value produced by adding 1 ml of distilled water instead of a substrate solution from the absorbance produced by adding a substrate solution.
[0029]That is, tyrosinase activity in case the Matsuki hide extract is 0 concentration was set to 100 (%), and the survival rate of tyrosinase activity when a sample solution is added was searched for by the ratio of absorption difference. A result is shown in drawing 1.
[0030]It is shown that the tyrosinase inhibitor in which the result of drawing 1 contains the Matsuki hide extract of this invention checks tyrosinase activity.
[0031](Example 1)
Face toilet glycerin 6g propylene glycol 4g oleyl alcohol 0.1g polyoxyethylene-lauryl-ether 1g ethanol 5g phenoxyethanol 0.1g ascorbic acid 1g Matsuki hide extract 2g purified water 80.8 g is mixed and agitated. It adjusted uniformly and the face toilet which checks an operation of a tyrosinase was obtained.
[0032]
(Example 2)

Emollient KURIMUMAIKUROKURA Stalin wax . 3 g Lanolin 3 g Vaseline 5 g Squalane . 9g olive oil 12g sorbitan sesquioleate 3 g Triolein acid polyoxyethylene sorbitan (20E.O.) 1g sorbitol 9g ascorbic acid 0.1g Matsuki hide extract 1g purified water 53.9 g Antiseptic Optimum dose Perfume Optimum dose. It mixed and agitated, and adjusted uniformly and the W/O type emollient cream which checks an operation of collagenase was obtained. Since this emollient cream has the tyrosinase inhibition effect in addition to a moisturizing effect and a keratin flexible effect, it is useful as skin external preparations.

[0033]

[Effect of the Invention]As mentioned above, since an operation of a tyrosinase can be checked with the Matsuki hide extract of natural material origin, generation of melanin can be controlled with tyrosinase inhibitor using this. The outstanding tyrosinase inhibition effect is acquired by making the Matsuki hide extract which contains 20 % of the weight or more and catechin for OPC 5% of the weight or more especially contain, and using as tyrosinase inhibitor. Since tyrosinase inhibitor is also that of natural product origin, it is safe, and the external preparations for the skins using this are also safe for it.

[Translation done.]